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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/691,051	10/22/2003	Ben K. Seon	03551.0137	6113

26712 7590 04/19/2005

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 04/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/691,051	SEON, BEN K.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-13 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-13 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Seon, B.
Date of Priority: 10/23/2002

DETAILED ACTION

Application Status

Currently, Claims 1-13 are pending and under consideration.

Species Election

During a telephone conversation with Ranjana Kadle on March 9, 2005 a provisional species election was made to prosecute the monoclonal antibody SN6j, claim 4. Affirmation of this election must be made by applicant in replying to this Office action.

Information Disclosure Statement

The Information Disclosure Statement filed on 10/25/2004 is acknowledged and has been considered. A signed copy of the IDS is attached hereto.

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Drawings/Specification

The disclosure is objected to because of the following informalities: The specification on page 4, lines 30+ appears to describe the details of Figure 7, i.e., tumors in individual human skin/SCID mouse chimeras that were treated with PBS, SN6j, CPA, or SN6j plus CPA. However, a comparison of the description and Figure 7 do not appear to coincide. For instance, what do the eight lines represent? Different concentrations? Appropriate correction is required.

Note: Applicants are reminded that no new matter should be introduced by amendment to the specification, see MPEP 35 USC 132. In addition, corrected drawing sheets in compliance with 37

CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inhibiting breast tumor growth in a mammal comprising the steps of administering to a mammal SN6j and a cyclophosphamide or doxorubicin, wherein the combination of SN6j and cyclophosphoamide or doxorubicin has a synergistic effect on breast tumor growth, does not reasonably provide enablement for a method of inhibiting growth in any and/or all tumors comprising the steps of administering to a mammal any and/or all anti-endoglin antibodies in combination with a chemotherapeutic agent, wherein the combination has a synergistic effect on the inhibition of the tumor growth. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands

states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The instant claims read on a method of inhibiting tumor growth in a mammal comprising administering any and/or all anti-endoglin antibody or antigen binding fragment thereof and a chemotherapeutic agent, wherein the combination of the anti-endoglin antibody or antigen binding fragment and the chemotherapeutic agent has a synergistic effect on the inhibition of tumor growth. Thus, the claims suggest that the combination of any and/or all anti-endoglins and a chemotherapeutic agent will have a synergistic effect on inhibiting the growth of any and/or all tumors.

The scope of the instant claims is not commensurate with the enablement of the instant disclosure, because practice of the claimed invention would require undue experimentation by an artisan of ordinary skill in the art. The instant specification is not enabling for method of inhibiting tumor growth in a mammal comprising administering any and/or all anti-endoglin antibody or antigen binding fragment thereof and a chemotherapeutic agent, wherein the combination of the anti-endoglin antibody or antigen binding fragment and the chemotherapeutic agent has a synergistic effect on the inhibition of tumor growth. The specification teaches that the present invention comprises administration of anti-EDG antibodies in conjunction with administration of chemotherapeutic agents, wherein the combination has a synergistic anti-tumor effect (page 5, lines 20-24). The specification further discloses (page 14, Example 5, Figure 3) suppression of established MCF-7 breast tumors by systemic administration of naked (unconjugated) mAbs, wherein out of SN6f, SN6j, SN6k, or SN6f plus SN6k, only SN6j and SN6k showed significant antitumor efficacy

and the combination of SN6f and SN6k showed and additive effect. Furthermore, the specification provides (pages 15-19, Example 6) a synergistic anti-tumor efficacy on MCF-7 breast tumors by the combination of SN6j mAb with cyclophosphamide or doxorubicin. Moreover, the specification discloses methods for evaluation of combination chemotherapy of malignant diseases (page 15, lines 30 to page 16, line 9). However, the specification appears to be silent on the synergistic anti-tumor efficacy by combination of any and/or all anti-endoglin antibodies and chemotherapeutics.

Although the specification discloses a synergistic relationship between the combination of one anti-endoglin antibody, SN6j, and cyclophosphamide or doxorubicin in MCF-7 human breast cancer cells, those of skill in the art would recognize the unpredictability that the combination of any and/or all anti-endoglin antibodies and a chemotherapeutic agent would display a similar synergistic relationship on any and/or all tumors. For example, Wiesenthal (http://weisenthal.org/feedback.html, 2/04/2002) discusses the question of synergy between drug combinations and diseases. In particular, Weisenthal states that "true synergy is rather uncommon in most adult tumors, wherein most drug combinations in disease such as lung cancer, breast cancer, and ovarian cancer are merely additive (whole equals the sum of its parts) and not synergistic." Moreover, Maier *et al.* (Anti-Cancer Drugs 1997; 8: 238-244) discloses the in vitro inhibition of endothelial cell growth by the anti-angiogenic drug AGM-1470 (TNP-470) and the anti-endoglin antibody TEC-11. Specifically, Maier et al found that the combination of AGM-1470 and TEC-11 did not produce an additive effect or a synergistic effect on growth cell inhibition, apoptosis or u-PA production (abstract, Figure 4 (A and B)). Thus, it does not appear that any and/or all anti-endoglin antibodies in combination with a chemotherapeutic agent are synergistic. Furthermore, Holmes (Seminars in Oncology 1996; 23: 46-56) examined the current status of paclitaxel combination therapy for the treatment of metastatic breast cancer and focuses on the phase I and phase II trials of paclitaxel in combination with established antineoplastic drugs for breast cancer including, but not limited to, cisplatin, 5-fluorouracil, monoclonal antibodies and gene therapy (abstract). The review article concludes that although combination therapy offers exciting possibilities of enhanced antitumor activity, the burden of proof will be to show that these combinations have increased anti-tumor activity, decreased toxicity, or both compared with single-agent paclitaxel (abstract). Lastly, in order for immunotherapy to be effective there needs to be a correlation between expression of EDG in normal versus tumor tissues. However, as pointed out by Seon (Int. J. Cancer 2002; 99: 310-311)

EDG is not a tumor-specific marker and that it is expressed in varying degrees in the vasculature of normal tissues (page 310, 2nd column, 1st paragraph). Therefore, in view of the teachings above, and the lack of guidance and or exemplification in the specification, it would not be predictable that the method would function as contemplated. Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-2, 4 and 6-9 are rejected under 35 U.S.C. 102(a) as being anticipated by Takahashi et al. (Cancer Research 2001; 61: 7846-7854).

In the instant case, the claims are drawn to a method for inhibiting tumor growth in a mammal comprising the steps of administering to the mammal an anti-endoglin antibody or antigen binding fragment thereof: and a chemotherapeutic agent wherein the combination of the anti-endoglin antibody or antigen binding fragment thereof and the chemotherapeutic agent has a synergistic effect on the inhibition of tumor growth (claim 1). With regards to the antibody, the antibody is further limited to a monoclonal antibody, wherein the monoclonal antibody is SN6j. The administration of the anti-endoglin antibody and the chemotherapeutic agent is further limited to simultaneously (claim 5) or sequentially (claim 6). The chemotherapeutic agent is further drawn to cyclophosphamide (claim 8 and 9).

Takahashi et al. discloses anti-angiogenic therapy of established tumors in human skin/severe combined immunodeficiency mouse chimeras by anti-endoglin (CD105) monoclonal antibodies. Specifically, the reference teaches a method of inhibiting tumor growth in a mammal comprising administering an anti-endoglin antibody, *i.e.*, SN6j, and a chemotherapeutic agent, *i.e.*, CPA (cyclophosphamide), wherein the combination of the anti-endoglin antibody and the chemotherapeutic agent has a synergistic effect on the inhibition of tumor growth (page 7851, Figure. 6). Takahashi et al. further teach that the administration of the agents followed an anti-

angiogenic schedule, wherein the SN6j antibody was administered every 3 days for the first five injections and every 4 days for the remaining 5 injections and CPA was administered every 4 days.

The following prior art is provided and made of record (although not relied upon) is considered pertinent to applicant's disclosure:

Seon, B.K. (U.S. 6,190,660, 2001) teaches anti-endoglin monoclonal antibodies and their use in anti-angiogenic therapy.

Thorpe et al. (U.S. 5,660, 827, 1997) teaches antibodies that bind to endoglin.

Biddle et al. (Leukemia Research 1989; 13: 699-707) teaches the in vitro and in vivo cytotoxic activity of anti-human leukemia monoclonal antibodies SN5c and SN6 daunorubicin conjugates.

Therefore, NO claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

BF

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
4/17/05